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MULTIPLE RISK FACTORS IN ENVIRONMENTAL CANCER

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For some environmental human cancer, it is now well established that interaction of multiple factors may significantly influence the degree of risk. This observation suggests a number of considerations for prevention of these neoplasms; in addition, it may have more immediate relevance to current proposals for surveillance and control.

MULTIPLE INTERACTION OF TWO AGENTS IN ETIOLOGY OF LUNG CANCER

Evidence of the carcinogenic potential of asbestos was provided over the period 1935-1965 for a number of neoplasms, including bronchogenic carcinoma [1-3], pleural and peritoneal mesothelioma [4-6], and gastrointestinal cancer [7]. It was found in 1967, however, that for the most important of these neoplasms—lung cancer—the risk did not depend on asbestos alone. Rather, if there were not concordance of *two* agents—cigarette smoking and asbestos—the tumor was uncommon [8].

In 1963, prospective observation was begun of 370 long-exposed asbestos workers in the New York metropolitan area. By April 30, 1967, no death from lung cancer had occurred among the 87 men with no history of cigarette smoking, despite their many years of occupational exposure to asbestos. In

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contrast, 24 deaths from lung cancer occurred among the 283 men with a history of cigarette smoking [8], although only 2.98 such deaths had been expected, given their smoking habits [9]. We suggested that the combination of the two factors—asbestos greatly increasing the lung cancer risk of cigarette smoking—had a sharp, multiplying effect. It was calculated that an asbestos worker who smokes cigarettes has eight times the risk compared to smokers of the same age who do not work with asbestos, and 92 times the risk of men who neither work with asbestos nor smoke cigarettes [8].

These findings were based on limited observations, especially with regard to nonsmokers. Additional investigations confirm the original conclusions [10].

The survivors of the original group of 370 men were followed to December 31, 1973. Altogether, 191 died from 1963 to 1973. Among the 87 men with no history of cigarette smoking, two deaths (of 41) occurred from lung cancer; both men smoked pipes or cigars. Among the 283 with a history of regular cigarette smoking, there were 150 deaths, 45 of lung cancer (Table 1).

A second, much larger, study was undertaken to investigate whether asbestos exposure without cigarette smoking truly did not increase the risk of lung cancer significantly, especially since such exposure was clearly associated with increased cancer risk at other sites (e.g., peritoneum, gastrointestinal tract) in nonsmokers. On January 1, 1967, we registered the entire membership of the insulation workers' union in the United States and Canada[1] and have observed the group since. When the cohort was enrolled, each man was asked to record his lifetime smoking habits. Of those enrolled, 9,590 indicated that they were either then smoking cigarettes or had previously smoked regularly; 609 had a history of smoking pipes and/or cigars but no cigarettes; and 1,457 had never smoked regularly at all. Smoking habits were not recorded for 6,144 men. Analysis of lung cancer deaths among the 17,800 men to December 31, 1972, showed that increased risk of this neoplasm was limited to asbestos workers who also had a history of cigarette smoking. Among the 9,590 cigarette smokers, there were 179 deaths from lung cancer (of 640 all told); of the 2,066 men with no history of cigarette smoking, only 2 (of 93 total) died of lung cancer (Table 2). Unfortunately, data are not yet available detailing lung cancer risk specifically for amount and nature of smoking, as were available through 1965 [9]. Nevertheless, using the earlier tabulations, these new findings again demonstrate that asbestos workers who do not smoke, or smoke only pipe and/or cigars, have about the same lung cancer risk as men not occupationally exposed to asbestos dust. However, exposure to asbestos dust greatly increases the lung cancer risk among cigarette smokers [11].

There is evidence [12] that uranium mining and cigarette smoking also interact as multiple factors. Moreover, an association between smoking and

[1] International Association of Heat and Frost Insulators and Asbestos Workers, AFL-CIO, CLC.

TABLE 1

Expected and observed deaths among 370 New York-New Jersey asbestos insulation workers, January 1, 1963–December 31, 1973, by smoking habits

History of	Number of men	Person-years of observation	Cause of death							
			Lung cancer			Pleural mesothelioma		Peritoneal mesothelioma		Asbestosis
			Expected[a]	Observed	Ratio					
	283	2,195	4.07	45	11.06	7		14		19

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	Number of men	Person-years of observation	Cause of death					
			Lung cancer			Pleural mesothelioma	Peritoneal mesothelioma	Asbestosis
			Expected[a]	Observed	Ratio			
History of cigarette smoking	283	2,195	4.07	45	11.06	7	14	19
Current smokers	181	1,443	2.48	32	12.09	6	7	12
Ex-smokers	102	752	1.59	13	8.18	1	7	7
No history of cigarette smoking	87	708	1.58	2	1.27	0	7	6
Never smoked	48	409	0.84	0	–	0	5	3
Pipe/cigar only	39	299	0.74	2	2.70	0	2	3

[a]Expected deaths are based upon age-specific white male death rate data of the U.S. National Office of Vital Statistics from 1963-71, disregarding smokings habits. Rates were extrapolated from 1972-73 from rates for 1967-71.

TABLE 2

Expected and observed deaths of lung cancer among 17,800 U.S. and Canada asbestos insulation workers, January 1, 1967-December 31, 1972; relation to cigarette smoking

	No. of persons	Deaths from lung cancer		
		Expected[a]	Observed	Ratio
Smoking habits not known	6,144	16.76	94	5.6
History of cigarette smoking	9,590	31.60	179	5.7
No history of cigarette smoking	2,066	7.51	2	0.3
Never smoked	1,457	4.40	1	0.2
History of pipe and/or cigar only	609	3.11	1	0.3

[a]Expected deaths based upon age-specific U.S. mortality rates for white males, disregarding smoking. Lung cancer estimates based on U.S. rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163 of the International Classification of Diseases and Causes of Deaths, 7th Revision.

radiation has been noted [13] among Hiroshima and Nagasaki atomic-bomb survivors, with lung cancer disproportionately increased among the radiation-exposed individuals who also had a history of cigarette smoking.

FACTORS ASSOCIATED WITH MODIFICATIONS OF RISK OF OCCURRENCE OF ENVIRONMENTAL CANCER

Intensity of Exposure

Although it is widely assumed, probably correctly, that intensity of exposure strongly influences human cancer risk [14], there are comparatively few direct data apart from cigarette smoking [9] and radiation [15] that support this belief or establish that a linear relationship exists. In large part, this stems from the absence of exposure data during the period when the implicated agent was unsuspected of carcinogenicity. Nevertheless, broad approximations have sometimes been made, either by reconstruction [16] or by comparison [17] of

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stances. Despite this uncertainty, it is
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World War II. More than 25 percent
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industrial hygiene precautions were
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Lung cancer then became common,
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Deaths from lung cancer		
Expected[a]	Observed	Ratio
16.76	94	5.6
31.60	179	5.7
7.51	2	0.3
4.40	1	0.2
3.11	1	0.3

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presumed exposures in occupational, neighborhood, and family contact circumstances. Despite this uncertainty, it is probably fair to conclude, at least over a considerable spectrum of exposure intensity, that cancer risk varies directly with exposure. In addition, this relationship may be used in predicting and defining high-risk groups, including the likelihood of a greater incidence of cancer and, often as a corollary, the appearance of some of the tumors after shorter induction periods.

Clearly the influence of exposure intensity is difficult to distinguish from variations in carcinogenic potential of agents or from multiplicative, additive, or less than additive effects of two or more coexisting agents. Further, some carcinogenic agents have nonneoplastic toxic effects that may be competitive with the cancer risk. Two important practical examples can be given. Verification of the cancer risk of occupational exposure to asbestos was delayed in Germany because of the extraordinary death rates from pulmonary fibrosis and cor pulmonale (asbestosis) resulting from the very poor hygiene conditions in East German (Dresden) factories in the difficult period immediately after World War II. More than 25 percent of deaths were caused by asbestosis, and many of the victims died before they reached the cancer-risk decades. Once industrial hygiene precautions were taken, deaths from asbestosis diminished to 3 percent, and workers lived well beyond the 20-year-from-onset point. Lung cancer then became common, with more than 20 percent of asbestos worker deaths so related [18].

We may see a similar competitive risk in the case of vinyl chloride angiosarcoma [19, 20], where nonneoplastic liver disease may be disabling or fatal [21-23] before the induction period of angiosarcoma has run its course.

In instances in which a carcinogenic agent can produce neoplasms at more than one site, again there can be variations in levels of risk for each tumor. Thus, the induction period for asbestos lung cancer seems shorter than for either pleural or peritoneal mesothelioma. We found this true in two cohorts of asbestos workers [24]. In one, shown in Table 3, composed of all 632 union asbestos insulation workers in the New York metropolitan area on January 1, 1943, and considering only deaths more than 20 years from onset of work, we found that in the first decade, 13 (15.7 percent) deaths were due to lung cancer and only 2 (2.4 percent) to mesothelioma. In the second decade, the percentages were much the same for the 170 deaths (29 cases or 17.1 percent vs. 5 cases or 2.9 percent). In the last 11 years, however, the percentages came closer together (191 total deaths, with 47 lung cancers or 29.8 percent, and 28 mesotheliomas or 14.7 percent).

The same tendency was observed in the experiences of another cohort, composed of 933 amosite asbestos factory workers first employed from 1941 to 1945 (Table 4). To 1962, there were 257 deaths with 31 or 12.1 percent from lung cancer; only one death from mesothelioma occurred. From 1963 to

TABLE 3

Expected and observed number of deaths among 623 New York-New Jersey asbestos insulation workers January 1, 1943-December 31, 1973, 20 or more years after onset of first exposure to asbestos.[a]

Cause of death	1943-1952			1953-1962			1963-1973			Total 1943-1973		
	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio
Total deaths–all causes	88.22	83	0.94	111.05	170	1.53	101.38	191	1.88	300.65	444	1.48
Cancer–all sites	13.02	30	2.30	18.75	65	3.47	19.49	103	5.28	51.26	198	3.86
Lung cancer	1.83	13	7.10	4.20	29	6.90	5.65	47	8.32	11.68	89	7.62
Pleural mesothelioma[b]	n.a.	1	—	n.a.	2	—	n.a.	7	—	n.a.	10	—
Peritoneal mesothelioma[b]	n.a.	1	—	n.a.	3	—	n.a.	21	—	n.a.	25	—
Cancer of the stomach	2.13	2	0.94	1.87	10	5.35	1.10	6	5.45	5.10	18	3.53
Cancer of the colon, rectum	2.22	7	3.15	2.74	9	3.28	2.54	6	2.36	7.50	22	2.93
Asbestosis[b]	n.a.	1	—	n.a.	11	—	n.a.	25	—	n.a.	37	—
All other causes	75.20	52	0.69	92.30	94	1.02	81.89	63	0.77	249.39	209	0.84

[a]632 members were on the union's rolls on January 1, 1943. Nine died before reaching 20 years from first employment. All others entered these calculations upon reaching the 20-year from onset of first exposure point. Expected deaths are based on white male age-specific death rate data of the U.S. National Office of Vital Statistics from 1949-71. Rates were extrapolated for 1943-48 from rates for 1949-55, and for 1972-73 from rates for 1967-71.

[b]U.S. death rates not available, but these are rare causes of death in the general population.

TABLE 4

Expected and observed deaths among 933 amosite asbestos factory workers first employed 1941-1945, and observed to December 31, 1973, by time periods.[a]

Cause of death	Before 1953			1953-1962			1963-1973			Total 1941-1973		
	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio
Total deaths–all causes	49.22	95	1.20	111.79	162	1.45	128.45	267	2.08	319.46	524	1.64
Cancer–all sites	11.90	15	1.35	19.36	50	2.58	24.13	98	4.06	54.58	163	2.99
Lung cancer	1.74	3	1.72	4.51	28	6.21	7.10	53	7.46	13.35	84	6.29
Pleural mesothelioma[b]	n.a.	1	—	n.a.	0		n.a.	4	—	n.a.	5	—
Peritoneal mesothelioma[b]	n.a.	0	—	n.a.	0	—	n.a.	6	—	n.a.	6	—

Cancer of the colon, rectum	2.22	7	3.15	2.74	9	3.28	2.54	6	2.36	7.50	22	2.93
Asbestosis [b]	n.a.	1	—	n.a.	11	—	n.a.	25	—	n.a.	37	—
All other causes	75.20	52	0.69	92.30	94	1.02	81.89	63	0.77	249.39	209	0.84

[a] 632 members were on the union's rolls on January 1, 1943. Nine died before reaching 20 years from first employment. All others entered these calculations upon reaching the 20-year from onset of first exposure point. Expected deaths are based on white male age-specific death rate data of the U.S. National Office of Vital Statistics from 1949-71. Rates were extrapolated for 1943-48 from rates for 1949-55, and for 1972-73 from rates for 1967-71.

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	Before 1953			1953-1962			1963-1973			Total 1941-1973		
Cause of death	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio
Total deaths—all causes	49.22	95	1.20	111.79	162	1.45	128.45	267	2.08	319.46	524	1.64
Cancer—all sites	11.90	15	1.35	19.36	50	2.58	24.13	98	4.06	54.58	163	2.99
Lung cancer	1.74	3	1.72	4.51	28	6.21	7.10	53	7.46	13.35	84	6.29
Pleural mesothelioma [b]	n.a.	1	—	n.a.	0	—	n.a.	4	—	n.a.	5	—
Peritoneal mesothelioma [b]	n.a.	0	—	n.a.	0	—	n.a.	6	—	n.a.	6	—
Cancer of the stomach	1.69	3	7.78	1.86	4	2.15	1.34	3	2.24	4.89	10	2.04
Cancer of the colon, rectum	1.82	2	1.10	2.74	5	1.82	3.09	9	2.91	7.65	16	2.09
All other cancer	5.25	6	1.14	9.11	13	1.12	11.53	23	1.99	25.89	42	1.62
Asbestosis [b]	n.a.	3	—	n.a.	8	—	n.a.	16	—	n.a.	27	—
All other causes	68.13	77	1.13	92.43	104	1.13	104.32	153	1.47	264.88	334	1.26

[a] Expected deaths are based upon white male age-specific death rate data of the U.S. National Office of Vital Statistics from 1949-71. Rates were extrapolated for 1941-48 from rates for 1949-55, and for 1972-73 from rates for 1967-71. 933 men were employed. In 5 cases, ages were not known and these men have been excluded from these calculations. 881 men were traced to death or to December 31, 1973. 47 men were partially traced and remain in the calculations until lost to observation.

[b] U.S. death rates not available, but these are rare causes of death in the general population.

1973 53 of 267 deaths were due to lung cancer (19.9 percent), but now 10 deaths were due to mesothelioma.

Duration from Onset of Exposure

By and large, cancers associated with exposure to identified environmental agents do not become clinically evident for 20 or more years after first exposure; often the elapsed period is 30, 40 or more years. There are exceptions, of course, as with the broadened induction span seen with more intense exposure and consequent larger numbers of tumors [25], or perhaps with exposure at very early ages. Despite such variations, the 20-plus year "rule" holds rather well, for exposures as diverse as radiation [13], aniline bladder tumors [25], nickel refining [26], or asbestos exposure [27]. Considerable data are now available with regard to the latter. Thus, among the amosite asbestos factory workers, cancer increased considerably after the first 20 years (Table 4). In the asbestos insulation worker study (United States and Canada) mentioned above [27], both total cancer and lung cancer increases were limited until after the 20-year point (Tables 5 and 6); this limitation applied even when smoking was taken into account (Table 7).

TABLE 5

Expected and observed deaths among 17,800 asbestos insulation workers in the United States and Canada, January 1, 1967-December 31, 1972

	Duration from onset of exposure			
	Less than 20 years		More than 20 years	
Cause of death	Expected[a]	Observed	Expected[a]	Observed
Total deaths—all causes	203.90	249	756.12	1,109
Cancer all sites	30.42	64	145.13	511
Lung cancer	8.40	28	47.47	247
Pleural mesothelioma[b]	n.a.	2	n.a.	27
Peritoneal mesothelioma[b]	n.a.	3	n.a.	60
Gastrointestinal cancer	4.64	5	33.15	56
All other cancer	17.38	26	64.51	121
Asbestosis[b]	n.a.	7	n.a.	94
All other causes	173.48	178	610.99	504
Number of persons	12,681		5,119	

[a]Expected rates are based on age-specific white male death rate data of the U.S. National Office of Vital Statistics. Rates for 1972 were extrapolated from rates for 1967-71.

[b]U.S. rates are not available, but these are rare causes of death in the general population.

TABL

Deaths from lung cancer
insulation workers in t
January 1, 1967-Decemb
to elapsed period from o

Years from onset	Expecte deaths
< 10	0.56
10-14	1.97
15-19	5.87
20-24	9.55
25-29	10.70
30-34	8.20
35-39	4.68
40-44	4.84
45-49	4.51
50+	4.97
Total	55.87

[a]Expected deaths are based upon age-specific
Office of Vital Statistics. Rates for 1972 wer

It is likely that "duration from on
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the latter, interesting data have recent
asbestos factory workers first employ
the same factory, during the same year
one-third worked for 3 months or less.
third for a year or more. The group wa
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Our knowledge is still fragmentary
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) years	More than 20 years	
Observed	Expected[a]	Observed
249	756.12	1,109
64	145.13	511
28	47.47	247
2	n.a.	27
3	n.a.	60
5	33.15	56
26	64.51	121
7	n.a.	94
178	610.99	504
		5,119

le death rate data of the U.S. National
olated from rates for 1967-71.
causes of death in the general popu-

TABLE 6
Deaths from lung cancer among 17,800 asbestos insulation workers in the U.S. and Canada, January 1, 1967-December 31, 1972; relation to elapsed period from onset of work exposure

	Lung cancer		
Years from onset	Expected deaths[a]	Observed deaths	Ratio
< 10	0.56	0	—
10-14	1.97	5	2.5
15-19	5.87	23	3.9
20-24	9.55	34	3.6
25-29	10.70	56	5.2
30-34	8.20	60	7.3
35-39	4.68	29	6.2
40-44	4.84	27	5.6
45-49	4.51	19	4.2
50+	4.97	22	4.4
Total	55.87	275	4.9 (average)

[a]Expected deaths are based upon age-specific white male death rate data of the U.S. National Office of Vital Statistics. Rates for 1972 were extrapolated from data for 1967-71.

It is likely that "duration from onset of exposure" is, in some instances at least, a composite effect and includes both the influence of total exposure and that of the passage of time from first exposure (or, perhaps more accurately, from the time sufficient exposure has occurred to result in increased cancer risk). Total duration of exposure has clear influence, as observed with uranium mining [28], aniline bladder cancer [25] and asbestos exposure. With regard to the latter, interesting data have recently become available. Among the amosite asbestos factory workers first employed in the period 1941 to 1945 (all in the same factory, during the same year, with the same exposure), approximately one-third worked for 3 months or less, one-third for 3 to 11 months, and one-third for a year or more. The group was traced through 1973. Both cancer of all sites and lung cancer showed their greatest increase in the last group (Table 8).

Our knowledge is still fragmentary concerning the mechanisms of cancer induction which influence these effects. We have inadequate information, for example, about tissue residence of various carcinogenic agents. Tissue burden

TABLE 7

Expected and observed deaths from lung cancer among 17,800 asbestos insulation workers in the U.S. and Canada, January 1, 1967-December 31, 1972, by duration from onset of work and cigarette smoking.

Smoking history	Years from onset of asbestos work: < 20 years Expected [a]	< 20 years Observed	< 20 years Ratio	20 or more years Expected [a]	20 or more years Observed	20 or more years Ratio	Total Expected [a]	Total Observed	Total Ratio
Smoked cigarettes	4.95	13	2.6	26.65	166	6.2	31.60	179	5.7
Never smoked cigarettes	0.87	0	–	6.64	2	0.3	7.51	2	0.3
Unknown	2.59	15	5.8	14.17	79	5.6	16.76	94	5.6
Total	8.41	28	3.4 (avg.)	47.46	247	5.2 (avg.)	55.87	275	4.9 (avg.)

[a] Expected deaths based on age-specific U.S. mortality rates for white males, disregarding smoking. Lung cancer estimates based upon U.S. rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163 of the International Classification of Diseases and Causes of Death, Seventh Revision, World Health Organization, Geneva, 1957. Included 609 men who smoked pipes or cigars.

TABLE 8

Expected and observed deaths subsequent to first year after onset of employment among 870 amosite asbestos factory workers first employed in 1941-45 and observed to December 31, 1973.

Cause of death	Distribution of duration of employment [a]: 3 months work or less Expected	3 months work or less Observed	3 months work or less Ratio	3-11 months work Expected	3-11 months work Observed	3-11 months work Ratio	1-year + work Expected	1-year + work Observed	1-year + work Ratio
Total deaths, all causes	99.75	112	1.12	94.34	170	1.80	110.55	216	1.95
Cancer—all sites	16.92	28	1.65	16.29	46	2.82	18.99	81	4.27
Lung cancer	4.13	16	3.87	4.00	16	4.00	4.64	49	10.56
Pleural mesothelioma [b]	n.a.	0	–	n.a.	2	–	n.a.	2	–
Peritoneal mesothelioma [b]	n.a.	0		n.a.	1		n.a.	4	–

Unknown	2.59	15	5.8	14.17	79	5.6	16.76	94	5.6
Total	8.41	28	3.4 (avg.)	47.46	247	5.2 (avg.)	55.87	275	4.9 (avg.)

[a]Expected deaths based on age-specific U.S. mortality rates for white males, disregarding smoking. Lung cancer estimates based upon U.S. rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163 of the International Classification of Diseases and Causes of Death, Seventh Revision, World Health Organization, Geneva, 1957. Included 609 men who smoked pipes or cigars.

TABLE 8

Expected and observed deaths subsequent to first year after onset of employment among 870 amosite asbestos factory workers first employed in 1941-45 and observed to December 31, 1973. Distribution of duration of employment [a]

	3 months work or less			3-11 months work			1-year + work		
Cause of death	Expected	Observed	Ratio	Expected	Observed	Ratio	Expected	Observed	Ratio
Total deaths, all causes	99.75	112	1.12	94.34	170	1.80	110.55	216	1.95
Cancer–all sites	16.92	28	1.65	16.29	46	2.82	18.99	81	4.27
Lung cancer	4.13	16	3.87	4.00	16	4.00	4.64	49	10.56
Pleural mesothelioma [b]	n.a.	0	—	n.a.	2	—	n.a.	2	—
Peritoneal mesothelioma [b]	n.a.	0	—	n.a.	1	—	n.a.	4	—
Cancer of stomach	1.46	1	0.68	1.47	3	2.04	1.73	5	2.89
Cancer of colon, rectum	2.38	4	1.68	2.27	7	3.08	2.67	5	1.87
Asbestosis [b]	n.a.	1	—	n.a.	2	—	n.a.	23	—
All other causes	82.83	83	1.00	78.05	122	1.56	91.56	112	1.22
Number of workers		249			294			327	
Person-years of observation		5,747			6,305			7,061	

[a]This table excluded 63 men. Ten died during first year of employment, 34 could not be traced after the first year, and 19 had prior occupational exposure to asbestos. Of the 870 men, 18 were partially traced and 16 had subsequent asbestos work. These remained in the calculations until lost to observation or until onset of subsequent asbestos work. Expected deaths are based on white male age-specific death rate data of the U.S. National Office of Vital Statistics, 1949-71. Rates were extrapolated for 1941-48 from rates for 1949-55 and for 1972-73 from rates for 1967-71.

[b]U.S. death rates not available, but these are rare causes of death in the general population.

of asbestos has been studied [29], and substances such as polychlorinated biphenyls, aldrin, dieldrin, and beryllium are found in tissues long after known exposure has ceased, but little can be concluded at present concerning the implications of such observations.

Specificity of Carcinogenic Effect

It is recognized, of course, that agents that classically produce neoplasms at one site may be potentially carcinogenic for other tissues as well. Cigarette smoking, for example, increases the risk of cancer of the larynx, buccal cavity, pharynx, esophagus, and bladder, as well as the lung. Bis(chloromethyl)ether affects the upper respiratory tract as well as the lung, and radiation can produce a number of neoplasms, sometimes varying with age at time of exposure, as with leukemia [30] and breast cancer [31]. Asbestos, as noted, is associated with a variety of tumors. Nevertheless, the various agents have predilections for certain sites. Mesothelioma brings asbestos to mind; nasal neoplasms, nickel carbonyl; and hemangiosarcoma, vinyl chloride. Skin cancer on the nose, hands, or ear lobes might suggest occupational exposure to coal tar. Indeed, such "signal" neoplasms have a long history, dating back to Percivall Pott's chimney sweeps' scrotal cancer [32], the precursor to more recent cancers of the same site with shale oil and mineral machine oils [33,34]. Some investigators have even proposed that, in the case of asbestos, the specificity for mesothelioma is greater for some kinds of asbestos than for others [35,36], although it has not been confirmed in extensive animal studies [37].

As expected, the converse is not true. Lung cancer may be associated with chromates [38], nickel, asbestos, hematite mining, bis(chloromethyl)ether [39], cigarette smoking, and radiation. Hemangiosarcoma of the liver may be associated with arsenic and thorotrast as well as vinyl chloride. Even mesothelioma, in at least 15 percent of instances, has no discernible asbestos etiology [40,41].

Agent specificity may even extend to multiple factor interaction. Hammond and colleagues [11] recently observed in asbestos workers a suggestive difference between the effects of cigarette smoking and cigar and pipe smoking. The latter indicated an influence on the risk of buccal, pharyngeal, and laryngeal cancer, but not for cancer of the lung or esophagus (Table 9).

IMPLICATIONS FOR CONTROL OF CANCER AMONG HIGH-RISK GROUPS

Identification of Groups at Anticipated High Risk of Cancer

It is now possible to predict with some assurance the approximate incidence of cancers of several sites in a number of identified groups, and to focus sharply

TABLE 9

Ratio of observed to expected deaths among 17,800 asbestos insulation workers in the U.S. and Canada, January 1, 1967-December 31, 1972[a]

Cause of death	History of Cigarette Smoking			History of Pipe and Cigar Smoking			Never Smoked		
	Expected[b]	Observed	Ratio	Expected	Observed	Ratio	Expected	Observed	Ratio
Lung cancer	31.60	179	5.7	3.11	1	0.3	4.40	1	0.2
Cancer of the esophagus	2.19	8	3.7	0.22	0	—	0.31	0	—
Cancer of the larynx	1.51	3	2.0	0.15	1	6.7	0.21	0	—
Cancer of the buccal cavity, pharynx	3.27	7	2.1	0.31	2	6.5	0.45	0	—

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Cancer of the larynx	1.51	3	2.0	0.15	1	6.7	0.21	0	–
Cancer of the buccal cavity, pharynx	3.27	7	2.1	0.31	2	6.5	0.45	0	–
	6.97	18	2.6	0.68	3	4.4	0.97	0	–
Deaths all causes	521.15	765	1.5	54.27	54	1.0	65.82	24	0.4
Number of workers		9,590			609			1,457	
Person-years of observation		55,526			3,525			8,622	

[a] Includes 6,144 workers for whom smoking habits were not known, with 35,191 person-years of observation.

[b] Expected deaths based upon age-specific U.S. mortality rates for white males, disregarding smoking. Lung cancer estimates based on U.S. rates for cancer of lung, pleura, bronchus and trachea, categories 162 and 163 of the International Classification of Diseases and Causes of Deaths, Seventh Revision, World Health Organization, Geneva, 1957.

on subgroups likely to have particularly high incidence. Thus, it may be insufficient to say that asbestos workers have a high risk of lung cancer. One estimate has it that whereas now some 200,000 workers are in the asbestos trades, another 800,000 who previously worked in these trades may have gone to other work or retired [42]. It is possible, however, to define which asbestos workers are especially liable to have lung cancer: those more than 20 years from onset, with a history of cigarette smoking, especially if there has been longer work history (Tables 1, 2, 7, and 8). Using such discriminatory criteria, we estimate that 10 to 20 percent of some groups will be of immediate concern. Similar considerations obtain with other agents and other neoplasms. Thus, vinyl chloride hemangiosarcoma of the liver also appears to have something like a 20-year induction period [43], and promises to be more common with more intense exposure (as with polymerization exposure); subgroups of individuals exposed to vinyl chloride who are at higher risk can be identified. Similar approaches may be utilized for uranium miners, workers exposed to benzidine, 2-naphthylamine, or a variety of other occupational carcinogens.

Evaluation of multiple risk factors may be useful in other than occupational groups as with transplacental effects that are either known to occur, as with diethylstilbestrol (DES) [44], or are suspected [19]. Cancer risks related to occupational agents also have been observed in other populations, as among family contacts ("conjugal disease") or among residents of neighborhoods around specific industrial plants [45]. The exposure of individuals in such subgroups is less intense than occupational exposure, but the other multiple-risk factors apply (duration from onset, smoking). In some instances, it may be possible to utilize "exposure markers," such as pleural plaques denoting prior asbestos exposure [46], to delimit further subgroups at higher risk.

Surveillance

As high-risk groups are defined by discriminatory application of multiple risk factors, surveillance may become possible at reasonable cost in personnel and facilities for several purposes. First, of course, is early diagnosis and improved prospects of cure and management. Examples would include chest X-ray and cytological studies of bronchial secretions for lung cancer, urine cytology for bladder cancer, liver studies including scans in vinyl chloride workers, hematological observation for workers exposed to benzene, vaginal examinations for female offspring of women receiving DES during pregnancy, skin examinations where appropriate, and even simple hemoglobin determinations for the modest increase in gastrointestinal cancer seen in asbestos workers.

Such surveillance would include the opportunity for possible reversal of at least some of the multiple risk factors. It may be that cessation of cigarette smoking will ameliorate the lung cancer risk of asbestos workers, uranium miners, or atomic-bomb survivors. Alcohol may add to the liver stress of vinyl chloride [47]; guidance during surveillance may be valuable.

Prospective surveillance of high-risk
retical benefits as well. The individuals
gain by concomitant studies designed t
cytological changes which may be pres
clinical disease. For example, what cher
exposed to benzidine who develop blad
do not [48]? Limited observations so fa
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What biochemical peculiarities distinguis
those who do not? High-risk groups will
testing the likely utility of large-scale sur
introduction, and perhaps even for trial
they become available.

The effectiveness of prospective sur
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be valuable.

Prospective surveillance of high-risk groups may also have important theoretical benefits as well. The individuals in the groups under observation stand to gain by concomitant studies designed to investigate metabolic, serological and cytological changes which may be present long before the earliest evidence of clinical disease. For example, what chemical changes are in the urine of workers exposed to benzidine who develop bladder cancer as compared with those who do not [48]? Limited observations so far have indicated that one in eight deaths among vinyl chloride polymerization workers was due to angiosarcoma [22]. What biochemical peculiarities distinguish those who develop the neoplasm from those who do not? High-risk groups will also provide a practical opportunity for testing the likely utility of large-scale surveillance techniques before their general introduction, and perhaps even for trials of prophylactic therapeutic agents, as they become available.

The effectiveness of prospective surveillance in terms of reversal or diminution of risk or of earlier diagnosis and treatment is not known—few experiences are at hand. The identification of multiple-risk factors and consideration of their utilization only make feasible exploration of such effectiveness. Nevertheless, the possibility that they may result in significant improvement in cancer control suggests that appropriate programs are now warranted.

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DISCUSSION

Dr. Higginson elaborated on the inappropriateness of average dose as a measure of carcinogenic effect. In Africa, for example, consumption of aflatoxin is either "spiking" or constant. Thus, residents of Kenya have an apparently steady intake of aflatoxin, while cultural differences in Swaziland produce sharp fluctuations in aflatoxin intake.

Dr. Rawson asked if patients with asbestosis are at poor risk for treatment because of impaired lung function. **Dr. Selikoff** responded that the tumors in asbestos workers tend to be peripheral, in the lower lobe, and sometimes operable. With mesothelioma, however, surgical intervention is often impossible and rarely attempted.

Dr. Nelson stressed the importance of studying the variables of intensity, duration of exposure, and postexposure intervals in evaluating groups at highest risk. Animal studies have revealed the dosage patterns most efficient in producing cancer, and these tend to fit the available human data.

W. Gary Flamm